Chapter 8
Drug- and Toxicant-Induced Liver Disease

A1. Develop definitions and standardization of procedures for diagnosis of hepatotoxicity and assignment of causality. The NIH-funded Drug-Induced Liver Injury Network (DILIN) has developed a rigorous process for assessing causality and a preliminary instrument that is being tested against other instruments in a prospective manner. The instrument needs further refinement and validation. (20%)

A2. Develop positive diagnostic assay for acetaminophen toxicity. An assay for acetaminophen adducts has been developed and is being tested for sensitivity and specificity in detecting acetaminophen-induced liver injury. (10%)

A3a. Develop *in vitro* or *in vivo* systems for study of allergic and non-allergic idiosyncratic hepatotoxicity. Mice given low doses of lipopolysaccharide have increased susceptibility to liver injury from several drugs known to cause idiosyncratic drug injury in humans, suggesting that low levels of hepatic inflammation predispose to this injury (Waring JF. *J Pharmacol Exp Ther* 2005; 316:1080). A Program Announcement on "Animal Models of NIDDK-Relevant Diseases" (PA-05-049) encourages research to develop animal models of hepatotoxicity. (10%)

A3b. Identify chemical substructures that are protoxicant and could be avoided in design of new drugs. Investigator-initiated work on an atlas of chemical substructures that are protoxicant has started. (0%)

B1. Develop a cohort of patients with well-characterized hepatotoxicity and controls with availability of serum, tissue, RNA, and DNA for genomic, transcriptomic, proteomic, and metabolomic studies. The DILIN network has enrolled more than 150 patients with idiosyncratic drug-induced liver injury into a database with careful collection of clinical information, serum, DNA and tissue. (10%)

B2a. Elucidate molecular mechanisms of common forms of hepatotoxicity. Efforts to define the molecular mechanisms of acetaminophen toxicity have dominated the research progress in this area with elucidation of the potential roles of stress kinases, DNA damage, ATP depletion, and the Bcl-2 family of apoptosis regulators. (10%)

B2b. Define incidence of drug-induced liver injury and the contribution of hepatotoxicity to the burden of acute and chronic liver disease in the United States. Funding for the Acute Liver Failure Study Group has been extended, and a pediatric component has been separately funded. Drug-induced liver disease continues to be the major cause of acute liver failure and secular trends suggest that it is increasing. Population-based studies have also been conducted in Spain, Switzerland, France and Sweden. (10%)

B3a. Define the role of the innate immune system in both allergic and non-allergic forms of hepatotoxicity. The role of the innate immune system (NK and

NKT cell function, interferon gamma and the Fas/FasL system) has been assessed in the acetaminophen injury model in mice. These studies need to be extended to other types of hepatotoxicity and to humans. (10%)

B3b. Develop an animal model of adaptation to hepatotoxicity to help define the genes necessary for the adaptive response. A Program Announcement has been published soliciting investigator-initiated research grants in this specific area ("Animal Models of NIDDK-Relevant Diseases," PA-05-049). (0%)

C1. Identify genetic factors that contribute to hepatotoxicity of several major forms of drug-induced liver disease. This area is the focus of extensive studies by industry and by the NIH-funded DILIN and Pharmacogenetics Research Networks, which are developing genetic screens for susceptibility to drug-induced liver injury. Several NIH- and industry-supported efforts are focusing upon transcriptomics and metabolomics evaluation of drug-induced toxicity in animal models. (0%)

C2a. Determine the efficacy of nonspecific therapy of hepatotoxicity with antioxidants or hepatoprotective medications. Both the adult and the pediatric Acute Liver Failure Study Groups are evaluating N-acetylcysteine as therapy for drug-induced and other forms of acute liver failure, the results of which should be available in 2 to 3 years. Trials of other agents have not been conducted. (0%)

C2b. Develop and assess biomarkers or metabolites to predict the development of hepatotoxicity, and to distinguish between established hepatotoxicity and transient, adaptive enzyme elevations. The DILIN Network as well as the Pharmacogenetics Research Networks are focused on these issues. This is also an area of interest to industry. Biomarkers are likely to be developed once cellular pathways of drug-induced liver injury are more fully defined. (0%)

C3. Develop molecular signatures that are diagnostic for major forms of hepatotoxicity. Investigator-initiated research studies as well as the Pharmacogenetics Research and DILIN Networks are focusing on developing resources and using transcriptomics, proteomics and metabolomics to provide insights into how drugs cause liver injury. An FDA Critical Path Initiative (Liver Toxicology Biomarker Study) has also begun, in order to encourage research in this area. (0%)

Figure 10. Estimated Progress on Drug- and Toxicant-Induced Liver Disease Research Goals, 2005 (Year 1)